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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,494	07/25/2000	MANFRED T. REETZ	STUDIEN-268-	6396

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EXAMINER	
PATTERSON, CHARLES L JR	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,494	REETZ ET AL.	
	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42-44 and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Nakanishi, et al. (N), Hirose, et al. (U-2) or Krainev, et al. (V-2) in view of Williams, et al. (A), Zhou, et al. (U), Leung, et al. (V), Cadwell, et al. (W) and Shinkai, et al. (X). and further in view of Armstrong, et al. (U-3), Kovach, et al. (V-3), Kim, et al (U-3) and Janes, et al. (X-3). This rejection is repeated for the reasons given in the last action. Applicants arguments have been carefully considered but do not overcome the instant rejection.

Applicants argue that (1) the cited references give no motivation to combine the references; (2) All of the claim limitations have not been dealt with and (3) that special consideration should be given to new claims 48-51.

(1) As stated in the action of 4/2/04, the five secondary references each teach a method of random mutagenesis to study what effect it has on a protein. In Williams, et al, column 1, lines 11-23 it is stated that while "site-directed mutagenesis…typically requires information on the structure-function relationship of the protein under study…random mutagenesis of the DNA region of interest coupled with adequate screening or selection procedures provides an alternative and general method for the generation of DNA, RNA or protein species with improved or novel functions in the absence of initial structural information". Leung, et al. state in the first paragraph in column 1 of page 11 that "[r]andom mutagenesis of the DNA region of interest

coupled to a screening system is therefore generally the method of choice for the study of a gene or its regulatory functions". Cadwell, et al. state in the first paragraph in the middle column on page 28 that [r]andom mutagenesis coupled with a screening method, is especially useful when functionally significant positions are not well known". This provides motivation to use random mutagenesis instead of the site directed mutagenesis taught by the primary references. Finally, as stated in the last action, the four tertiary references covering a period of 18 years show that one of ordinary skill in the art would know to use spectrophotometry as a well known method to measure the activity of hydrolases with respect to stereoselectivity or regioselectivity.

(2) Applicants argue that claim 45 what requires fragmenting the mutant genes and/or the starting genes and recombining them are not taught by the references. The references relating to DNA shuffling (Stemmer and Zhang, et al.) were dropped in the action of 8/18/04 because of applicants' arguments. They have been reinstated along with another reference in this action. Because of the new rejection, this action is being made non-final.

Applicant also argue that claims 44 and 47 require that the starting hydrolase has been previously mutagenized in a PCR reaction. As stated in the action of 8/14/04, column 4, lines 57-64 of Williams, et al., "there is a substantially linear correlation between the mutation frequency and the number of PCR cycles performed". On page 31, column 2 of Cadwell, et al. it is stated that "[a]n obvious way to increase the overall error rate of the PCR would be to carry out more reaction cycles". This covers the indicated portion of the argument to mutagenizing a prior mutagenized gene.

(3) Claims 48-51 require mutating a plurality of genes, transforming them into a plurality of organisms, screening the enzymes produced by these

organisms and identifying mutants having an improved stereoselectivity or regioselectivity. On page 9 of the instant amendment applicants point to the paragraph spanning pages 6-7 as the support for these claims in that it discloses preparing mutant hydrolase libraries which applicants characterize as containing a plurality of mutant hydrolases. It is agreed that "mutant hydrolase libraries" envisions a plurality of mutant enzymes, however it is pointed out that the specification does not teach mutating a plurality of different mutant genes (genes encoding different enzymes) and then trying to analyze them. Nakanishi, et al. state in the "Constitution" "replacing one or more amino acid residues" of the enzyme, Hirose, et al. state on page 1064, third paragraph that "[w]e prepared several [l]ipases [sic]" and Krainev, et al. state in the introduction that "mutations at the putative distal site of P450 1A2 affect this discrimination [and that] [w]e also examine a Lys250Leu mutant at one of the other putative distal sites". All of the recitations teach mutating a plurality of enzymes. Further, it is maintained that one of ordinary skill in the art would mutate more than one gene in order to try and obtain the desired mutants and would prepare libraries of them, absent a very convincing argument to the contrary.

Claims 45-47 and 50-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Nakanishi, et al. (N), Hirose, et al. (U-2) or Krainev, et al. (V-2) in view of Williams, et al. (A), Zhou, et al. (U), Leung, et al. (V), Cadwell, et al. (W), Shinkai, et al. (X), Stemmer (V-1 and W-2), and Zang, et al. (W-1) and further in view of Armstrong, et al. (U-3), Kovach, et al. (V-3), Kim, et al (U-3) and Janes, et al. (X-3).

All of the references except for Stemmer (V-1 and W-2), and Zang, et al. (W-1) are characterized *supra*. Stemmer (V-1 and W-2), and Zang, et al.

(W-1) each teach a method of mutating genes by using "DNA shuffling", i.e. digesting the gene with an enzyme into fragments and then reassembling the genes. It would have been obvious to one of ordinary skill in the art to use the instant method to mutagenize genes. Stemmer (V-1) states in the introduction that "[a]lthough recombination with a low level of point mutation, was long ago demonstrated to be a preferred method of multiple cycles of mutagenesis…so far no methods have been demonstrated for general, homologous recombination of DNA *in vitro* [and this DNA shuffling] is a technically simple approach". Zang, et al. teaches in the introduction that "[w]e obtained *in vitro* recombination of infrequent point mutation by a PCR-based technique called DNA shuffling…[and that this process] allows rapid combination of positive-acting mutations and simultaneously flushes out negative-acting mutations from the sequence pool". Therefore these stated reasons provide motivation to use this process for the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 571-272-0936. The examiner can normally be reached on Monday - Friday from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available

through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
May 11, 2006